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Citation for published version:

Li, Y, Wang, M, Gao, Y, Yang, W, Xu, Q, Eddleston, M, Li, L & Yu, X 2015, 'Abnormal pancreatic enzymes and their prognostic role after acute paraquat poisoning', *Nature*. <https://doi.org/10.1038/srep17299>

Digital Object Identifier (DOI):

[10.1038/srep17299](https://doi.org/10.1038/srep17299)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Publisher's PDF, also known as Version of record

Published In:

Nature

Publisher Rights Statement:

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SCIENTIFIC REPORTS

OPEN

Abnormal pancreatic enzymes and their prognostic role after acute paraquat poisoning

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Received: 08 April 2015

Accepted: 26 October 2015

Published: 25 November 2015

Ingestion of paraquat causes multi-organ failure. Prognosis is best estimated through measurement of blood paraquat concentrations but this facility is not available in most hospitals. We studied the prognostic significance of abnormal pancreatic enzymes for survival. Patients with acute paraquat poisoning were recruited. An extensive series of blood tests including serum amylase were serially checked. Patients were sorted according to their serum amylase activity (normal [<220 U/L], mildly elevated [220 to 660 U/L], elevated [>660 U/L]), and survival compared between groups. 177 patients were enrolled to the study, of whom 67 died and 110 survived. 122 (70.62%), 27 (15.25%) and 25 (14.13%) patients were in the normal, mildly elevated and elevated amylase activity groups, respectively. The case fatality in the elevated group was 100% compared to 17% in the normal group ($P < 0.001$). We found four independent factors for paraquat death prediction: amylase, PaCO_2 , leukocyte number, and neutrophil percentage. Models using pancreatic enzyme activity showed good prediction power. We have found that abnormal pancreatic enzymes are useful prognostic marker of death after acute paraquat poisoning. Including serum amylase activity into a prognostic model provides a good prognostication.

Although paraquat is a highly effective herbicide, it is lethal after ingestion with mortality being around 80% after confirmed exposure^{1,2}. The main cause of death is multi-organ failure including acute respiratory, renal and hepatic failure and cardiac injury^{2–5}. Although pancreatic injury has been reported after paraquat poisoning⁶, it is unclear how often and when pancreatic injury occurs and whether it has any prognostic value.

Single lab analyses, such as serum paraquat concentration^{1,7–9}, arterial lactate¹⁰, uric acid¹¹, lymphocyte and neutrophil count, and creatinine¹² have been used in risk stratification, and serum paraquat concentration has been thought as the most reliable parameter for prognosis prediction⁹. But it is difficult to extend the serum paraquat concentration technology to district hospitals because the high cost of the assay. Another potential indicator is the ingestion volume, which is affected by the difficulty of calculating it accurately and vomiting post-ingestion^{8,13}.

Acute physiology and chronic health evaluation 2 (APACHE 2)¹⁴, and sequential organ failure assessment (SOFA)¹⁵ scores had been used for the evaluation of critical patients. Some authors have studied their power in paraquat poisoning, showing APACHE 2 and SOFA to be helpful for paraquat poisoning mortality prediction^{16–19}. The Poisoning Severity Score (PSS) has been recommended for stratification

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of poisoned patients²⁰. But those scores are not easy for calculating in emergency department, where a simple and precise method of prognosis is needed.

We therefore prospectively studied pancreatic injury and other routine investigations in acute paraquat poisoning patients admitted to the first affiliated hospital of Zhengzhou University, a tertiary hospital in China. If independent risk factors can be found for prediction of death prediction, new models for prognosis prediction could be set up and compared with traditional score systems.

Methods

Patients admitted to the first affiliated hospital of Zhengzhou University from July 2013 to August 2014 were enrolled.

Inclusion criteria were: acute paraquat poisoning by ingestion within 72 hours; confirmed by the semi-quantitative urine paraquat test with positive result as the concentration was over 0.2 ug/mL (normal range 0–0.2 ug/mL)²¹; and consent from the patient or family. Patients were only enrolled if all 3 criteria were met.

The urine concentration was determined as the reported²¹: a standard line using urine from the healthy volunteer and the paraquat herbicide sample were drawn. Then put Na_2CO_3 and NaHCO_3 to the urine sample to make $\text{pH} > 9$. The urine was filtered with film, and put $\text{Na}_2\text{S}_2\text{O}_4$, and determine the urine paraquat concentration with spectrometry in 396 nm. Then an equal was set up: urine paraquat concentration (ug/ml) = $5.1014 \times \text{OD value}$, and with $R^2 = 0.9956$. Concentration of fresh urine from the patient was checked and calculated using the equal as above.

Exclusion criteria were: poisoned by routes other than ingestion; admitted more than 72 hours after ingestion; co-ingestion of other toxins; pregnant or lactating patients; cardiac arrest after poisoning; past medical history of pancreas, heart, liver, kidney, or central nervous system disease; or refused consent. Patients were excluded if any one of the above criteria occurred.

All the patients were treated according to guidelines published by the China Physician Association (2013 version)²². All the patients received a single gastric lavage with room-warmed water regardless of whether they had been previously lavaged during this exposure. Six grams of smectite powder was given every 4 hours for the first day after admission.

Methylprednisolone 15 mg/kg/d was given and reduced one week later by 40 mg every 3 days. Ten to 15 mg/kg/d cyclophosphamide was administered for one week. Hemoperfusion was performed within 1 hour of admission for four hours, and repeated once a day for at least three days. Hemofiltration was performed for acute renal failure.

Patients were put on oxygen only when the pulse saturation was below 70% (or arterial oxygen pressure below 50 mm Hg), and dyspnea discomfort and signs had occurred.

The basic data of the patients were recorded, including age, gender, ingestion volume and time, the time of hemoperfusion and vital signs at admission. If the ingestion volume was unknown, it was estimated by mouthfuls (one female mouthful 30 ml, one male mouthful 40 ml).

Blood was drawn on the first, third, seventh and ninth day after admission for the routine lab tests, which included: serum amylase and lipase; platelet, leukocyte, lymphocyte and neutrophil percentage, plateletcrit, mean platelet volume; PaCO_2 and PaO_2 , arterial lactate; alanine transaminase (ALT), total bilirubin, lactate dehydrogenase, γ -glutamyl transpeptidase; blood urea nitrogen and creatinine; cystatin C; creatine kinase, creatine kinase-MB. Glasgow coma score (GCS), APACHE 2, SOFA and PSS score were recorded for each patient after admission.

Based on the admission serum amylase activity, which normal range is 0–220 U/L, patients were sorted into three groups: normal group, with amylase lower than 220 U/L; mild amylase elevation group, with amylase between 220 U/L and 660 U/L; amylase elevation group, with amylase over 660 U/L.

Ethical statement. All experimental protocols of the study were approved by the First Affiliated Hospital of Zhengzhou University's ethics committee on June 29, 2013 with the number of ZY20130629, and were performed strictly as approved. The methods were carried out in accordance with the approved guidelines. Written informed consent was obtained from all enrolled patients.

Statistical analysis. Data were expressed as median (25 quantile, 75 quantile) or as a percentage. Each variable above was compared between the survival and the deceased. Lifetest was used to compare survival curves of different pancreas groups. In order to analyze the prediction of the death of paraquat poisoning, logistic regression model and receiving operating characteristic (ROC) curve²³ analyses were performed. Cox regression analysis was performed in order to build the prognostic indicator (PI) system. All *p*-values were two tailed, with statistical significance defined as $p < 0.05$. All statistical analyses were performed with SAS 9.2 software.

Result

Of 258 patients with acute paraquat poisoning admitted to our hospital, 177 had laboratory confirmation of paraquat ingestion within 72 hrs and were enrolled into the study (Fig. 1). There was a small male excess (97, 54.8% male vs 80, 45.2% female); their age ranged from one year to 66 years. The median ingestion volume was 30 (interquartile range 10 to 60) mL, with median urine paraquat concentration

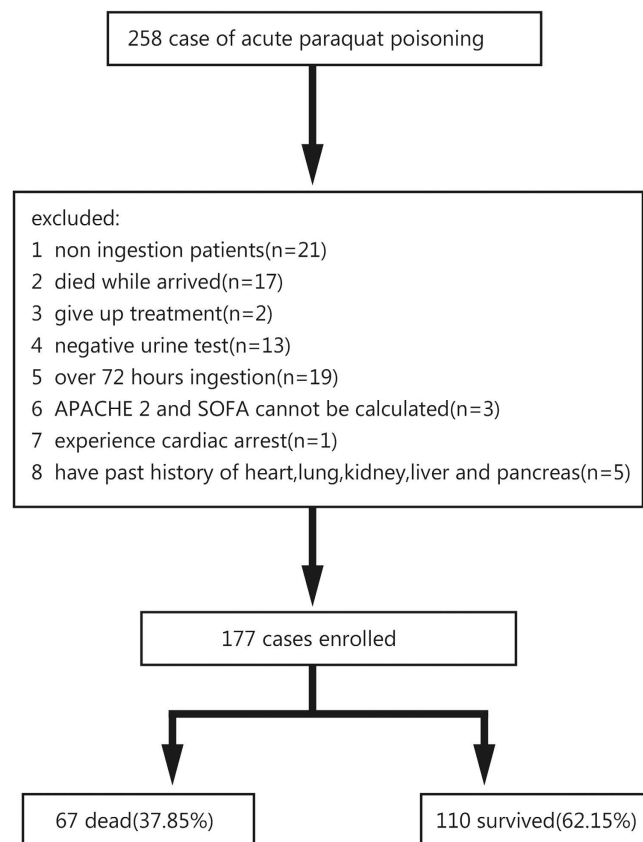


Figure 1. Flow chart of study recruitment.

Characteristic	value
Age (year, median IQR)	29 (22 to 43)
Male (%)	97 (56.1%)
GCS (median, IQR)	15 (14 to 15)
Ingestion volume (mL, median IQR)	30 (10 to 60)
Urine paraquat concentration (ug/mL, median IQR)	27.3 (5.1 to 72.9)
Delay from ingestion to admission (hr, median IQR)	7 (5 to 10)

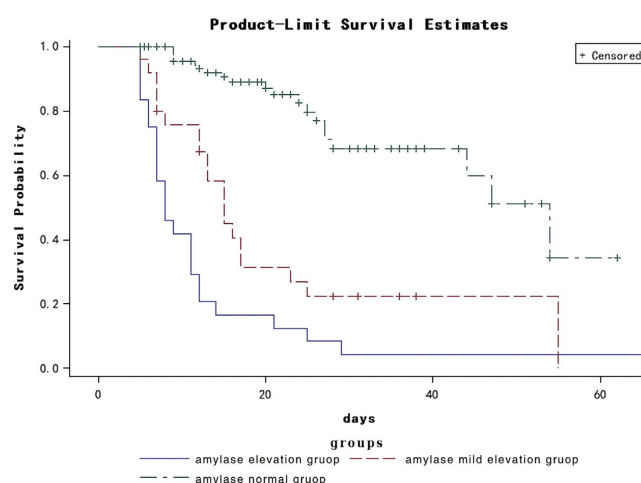
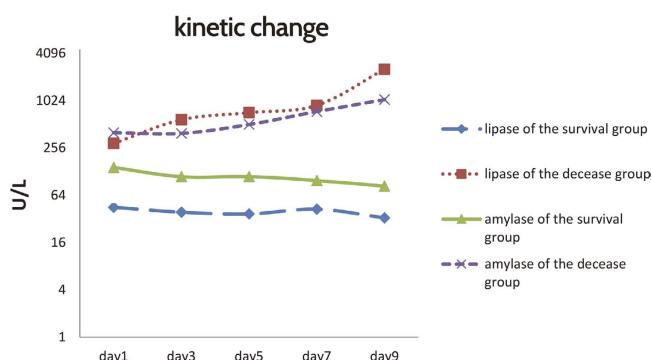
Table 1. Patient demographics (n = 177). IQR: interquartile range.

of 27.3 (interquartile range 5.1 to 72.9) ug/mL. Patients were admitted a median of seven (interquartile range 5 to 10) hours after ingestion (Table 1).

Almost one third of patients had deranged pancreatic enzymes on admission. Twenty-seven patients had a mild elevation in amylase, while 25 had greater elevation (>660 U/L) and 125 had normal amylase. The case fatality in the elevation group was 100%, compared to 17% in the group without pancreatic enzyme changes (Table 2). Survival curves are depicted in Fig. 2, showing that deaths occurred later in the normal group, while deaths occurred most quickly in the elevation group, with significance difference among groups ($P < 0.001$).

An additional 14 patients developed pancreatic enzyme increase over the subsequent nine days, making a total of 66 patients (on admission, 27 had mild increase and 25 had greater increase; 14 increase in the following days.) with deranged pancreatic enzymes. These patients were sorted into a survival group (48 patients) and a deceased group (18 patients). The daily change of serum lipase and amylase is shown in Fig. 3. Both increased from admission until death; by contrast in the survival group they increased only a little and then remained at around this activity until discharge ($P < 0.001$ for the difference between groups). The kinetic changes of lipase were coincide with those of amylase, and there is positive relationship between the two pancreatic enzymes ($r = 0.491$, $P < 0.0001$).

Group	Number (%)	Deaths (% of all deaths)	Case fatality (95% CI)
Normal	125 (70.6)	21 (31.3)	0.17 (0.11 to 0.24)
Mildly elevated	27 (15.3)	21 (31.3)	0.78 (0.59 to 0.89)
Elevated	25 (14.1)	25 (37.3)	1.00 (0.87 to 1.00)

Table 2. Frequency of pancreatic injury.**Figure 2.** Survival curves for the groups according to the level of amylase. Blue solid line: elevated group; red dotted line: mildly elevated group; green dotted line: normal group.**Figure 3.** Daily kinetic change of amylase and lipase according to outcome. Red dotted line: lipase of the deceased group; purple dotted line: amylase of the deceased group; green solid line: amylase of the survival group; blue dotted line: lipase of the survival group. There were 48 patients in the survival group, and 18 patients in the deceased group.

No patient had abdominal pain. Imaging showed no evidence of pancreatic injury. Abdominal ultrasound was done on all patients, without finding of any abnormal results. A CT scan was done on patients with deranged pancreatic enzymes, but again no abnormality was noted. However, patients with deranged pancreatic enzymes developed abdominal distention, which was worse in those who died.

Univariate logistic regression analysis was done to select the predictors of death paraquat poisoning, and 10 predictors had P value lower than 0.05 were found (affiliated Table). Multivariate logistic regression analysis was performed to find out the independent index for the death, and leukocyte, amylase, neutrophil percentage and PaCO₂ was chosen finally.

ROC curve was drawn and area under the curve (AUC) were calculated for the four independent factors (Fig. 4). Neutrophil percentage had the highest AUC of 0.9229, while amylase had the lowest AUC of 0.8160 among the four factors.

We choose lipase and amylase in the equal of PI 1 and model was set up by Cox regression. PI 1: $h(t) = h_0(t) \exp(0.0003571 * \text{lipase} + 0.0004273 * \text{amylase})$

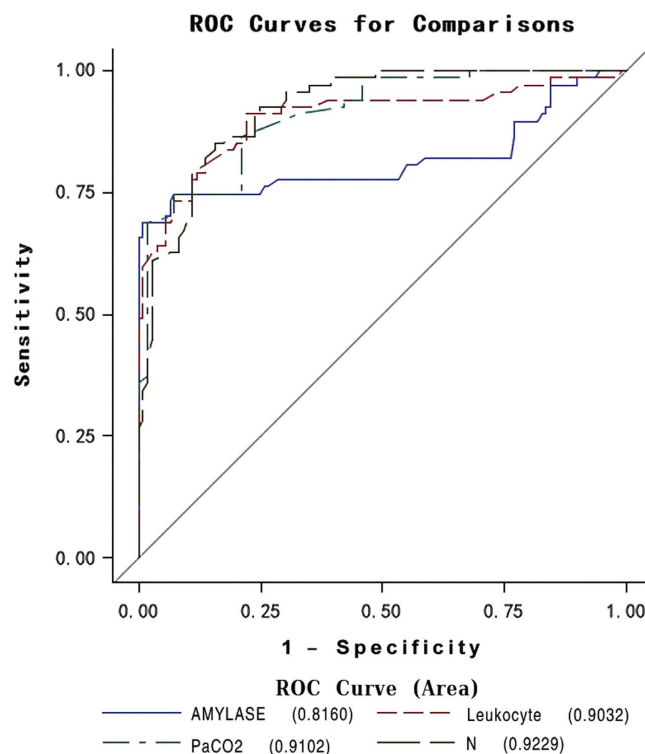


Figure 4. ROC for the factors with significant difference in the multi-logistic Regression.

	Best cutoff (>)	Sensitivity (%)	Specifity (%)	Diagnosis Accuracy (%)	Youden index	AUC
SOFA	9	77.61	87.27	83.62	0.65	0.889
PSS	3	100	98.18	98.87	0.98	0.990
APACHE2	14	97.01	93.64	94.92	0.91	0.975
PI1	0.46	77.61	99.08	90.1	0.767	0.903
PI2	0.18	100	96.33	99.6	0.963	0.996

Table 3. Comparison of the prediction model with traditional scores. PI1: model incorporating pancreatic enzymes including amylase and lipase. PI2: model incorporating leukocyte, amylase, neutrophil percent (N%), and PaCO₂.

$$PI1 \text{ of pancreatic enzymes} = (0.0003571 * \text{lipase1} + 0.0004273 * \text{amylase1}).$$

Because the model above had not added other independent factors inside, we add neutrophil percentage, PaCO₂, leukocyte count, and reserved amylase for pancreatic enzyme (excluding lipase). The second model, PI 2 based on the pancreas enzyme and other important factors, was made.

$$h(t) = h_0(t) \exp(0.08749 * N1 + 0.0004138 * \text{Amylase} + 0.05096 * \text{WBC1} - 0.12222 * \text{PaCO}_2).$$

$$PI2 = (0.08749 * N1 + 0.0004138 * \text{Amylase} + 0.05096 * \text{WBC1} - 0.12222 * \text{PaCO}_2).$$

It was found that the PI 2 is the most precise one compared with the three traditional scores and PI 1, with AUC of 0.996 (Table 3, affiliated Figs 1 and 2).

Discussion

In this study, we have focused on pancreatic injury in acute paraquat poisoning. The main findings of our study are: 1) pancreatic enzymes elevation occurs in paraquat poisoning; 2) the more severely deranged the pancreatic enzymes, the worse the outcome; 3) a prediction model utilizing amylase and leukocyte, neutrophil percentage and PaCO₂, is much precise than other commonly used scores.

Acute paraquat poisoning can lead to multiple organ dysfunction syndrome (MODS), including lungs, gastrointestinal tract, kidney and liver, which commonly leads to death. Some previous studies had reported the abnormal pancreatic enzymes, but few studies have focused on these changes or pancreas^{6,10,24–29}. For example, a similar finding had been reported that amylase together with PaCO₂, and

leukocyte has been found to be associated with the survival. But this paper had not focused on the clinical importance of amylase and had not set up a model based on these factors for survival prediction as us³⁰.

The first evidence of pancreatic injury came from an autopsy report, which found an evident mild pancreatic change in one case³¹. Wang and colleagues reported a fatal case, in which serum amylase and lipase was increased several hours after ingestion and increased further thereafter. Afterwards, the lungs, kidney, liver and heart were involved till to the death⁶. So the authors thought that pancreas can be injured after acute paraquat poisoning and was related to the death.

A retrospective Chinese study of 502 cases admitted within 24 hours of paraquat ingestion reported that 180 (35.86%) cases with abnormal pancreatic enzymes, 171 (95%) died, with only 9 (5%) being cured²⁸. So we can see that there are high rate of abnormal pancreatic enzymes, which increase the death risk. But this report did not study the kinetic changes of pancreatic enzymes because it was a retrospective study.

Abnormal pancreatic enzymes have been observed in 10 cases in English literature²⁷. In a study of retrospective 272 cases, Lee and colleagues showed that pancreatic enzymes were higher in patients who died than those who survived (median amylase 138.5 IU vs. 87 IU, lipase 37 IU vs 29 IU, respectively, both $P < 0.0001$)¹⁰. Another retrospective study of 296 cases found that elevated amylase activity was a significant predictor of survival using univariate analysis (deaths 480.5 ± 679.8 IU vs survivors 168.0 ± 181.9 IU, $P < 0.01$)²⁶.

A single retrospective study has looked at pancreatic enzymes in 34 patients who survived paraquat poisoning²⁵, which was the first study to focus on the abnormal pancreatic enzymes after paraquat ingestion. Pancreatic enzymes were elevated in 7 (20.6%) cases, and peaked on the seventh day; the extent of increase was positively related to the serum paraquat concentration on the fourth and seventh days ($p < 0.05$). CT examination was normal in all these patients, so the elevation was considered to be an inflammatory reaction by the authors²⁵.

47 cases study in Chinese literature show that no patients had abnormal pancreatic enzymes after mild paraquat poisoning, while 58.5% had such increase after severe poisoning³². The increase rate in our study was 30%, which is higher than GIL HW's report about alive paraquat patients alone (around 20%)²⁵. The reason for the higher abnormal pancreatic enzymes rates in our study may be that ours are assumed more severe than theirs and is more close to the true clinical status.

Diagnostic criteria for acute pancreatitis include acute abdominal pain, a greater than 3 fold increase in pancreatic enzyme activity, and abnormal changes noted on ultrasound or CT scan. If two of the criteria were met, the diagnosis can be made³³.

In view of one criteria of 3 fold increase amylase for acute pancreatitis diagnosis and the normal range of amylase is our hospital (0–220 U/L), we sorted the patients into three groups, i.e. normal (< 220 U/L), 3 fold increases which satisfied the criteria for acute pancreatitis diagnosis (> 660 U/L), increase but not satisfied for the diagnosis of 3 fold (> 220 U/L, but < 660 U/L). The best prognosis was found in normal group, and the worst in the elevation group. Because pancreatic enzymes elevation was found without abdominal pain and change on imaging, acute pancreatitis cannot be diagnosed.

The mechanism of the abnormal pancreatic enzymes changes is unclear. In the past, splanchnic hypoperfusion, drug adverse effects, stroke, cranial injury and others had been reported as the factors contributing to the changes³⁴. The sources of amylase are the pancreas and salivary glands, intestine, and other tissues in small quantities, which may be identified by electrophoresis using isoform differentiation³⁵. There are several lipases in the human body too, including lingual, pancreatic, lipoprotein, intestinal, and hepatic lipase. Between 11 and 12.5 percent of patients admitted to the hospital with non-pancreatic abdominal pain have an elevated serum lipase³⁶. Because no abdominal pain and image changes can be found in our cases, so pancreatic injury or pancreatitis cannot be diagnosed at this stage. The abnormal pancreatic enzymes changes can be derived from the pancreas as well as the saliva, the intestine in paraquat poisoning, which need future exploration.

In view of the abnormal pancreatic enzymes changes in our study, we aimed to develop a prognosis model based around pancreatic enzymes. In the past, many experts had tried to find some single factors. Serum paraquat concentration is a good prognostic factor^{37,38}. For example a recent report has retrospectively review 2136 paraquat ingestion patients, and set up three prediction models. The most powerful model of the three was composed of serum paraquat level and the ingestion time. But the limitations of the study were its retrospective design and the uneasy reach of serum paraquat test in clinical practice³⁹.

Because the technology for performing the serum paraquat analysis is missing from most countryside hospitals, lactate¹⁰, uric acid¹¹, lymphocyte and neutrophil count, and creatinine¹² have been proposed as useful prognostic factors. But because single factors are easier to lead to errors, scores had been used, such as APACHE 2 and SOFA scores, and PSS^{20,16–19}. But these three scores are time costing and need multiple laboratory results. Some easier scores, such as severity indexes related with serum paraquat concentration⁴⁰ and the respiratory index (RI: $A-aDO_2/PO_2$ and the RI-time⁴¹ had been evaluated, but they have not been widely accepted. So the importance of finding easily applied practical scores requires attention.

In view of the unstable power of the single factors and the complex of the traditional scores, and different from most of the above retrospective study, our report is prospective design and our model is based on the most routine test in clinical work³⁹.

We used multivariate logistic regression and identified four independent factors including leukocyte and neutrophil counts, PaCO₂ and amylase for prediction of fatal paraquat poisoning. Prediction models were set up based on the pancreatic enzymes alone (PI 1) or on four independent factors (PI 2). The power of our prediction models was compared to traditional scores: PI 2 was found having the greatest power. In addition, the four lab exams in the PI 2 model are easy to do in nearly all the hospitals, so PI 2 model is recommended in future clinical work practice.

Limitations

The serum paraquat cannot be checked and only urine paraquat level was checked in our study. The urine paraquat result may be influenced by the renal function⁷, so our PI 2 model needs the comparison of its power with serum and urine paraquat result in the future.

The cause of the abnormal pancreatic enzymes changes is unclear, and the pancreatic injury is needed to be confirmed in the future.

Larger sample are needed to validate our abnormal pancreatic enzymes changes and judge the power of our models.

Conclusion

Acute paraquat poisoning can cause abnormal pancreatic enzymes changes which is often detectable soon after the ingestion and on admission to hospital. The more elevated the enzymes, the worse outcome of the patients. Amylase is an independent prognostic marker. Models including pancreatic enzymes have good prediction power, and are easier and simpler than the traditional scores.

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Acknowledgements

Funding: This study was supported by the National Key Department Foundation of Health Ministry (No. 2012-650,649).

Author Contributions

Y.L., X.Y. and Y.G. set up the idea for writing the paper, L.L. and Y.G. collected the data regarding the paper, W.Y., M.W. and Q.X. analyzed the data, Y.L. and Y.G. wrote the original paper in English, and M.E. revised the paper, worked on the English, and made the final version of the manuscript. All authors reviewed the final version of manuscript.

Additional Information

Competing financial interests: The authors declare no competing financial interests.

How to cite this article: Li, Y. *et al.* Abnormal pancreatic enzymes and their prognostic role after acute paraquat poisoning. *Sci. Rep.* **5**, 17299; doi: 10.1038/srep17299 (2015).



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